UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No.: 0053852

MEMORANDUM

DATE: November 10, 2005

SUBJECT: **IODOMETHANE:** Report of the Cancer Assessment Review Committee
PC Code: 000011

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)

TO: Elizabeth Méndez, Toxicologist/Risk Assessor (RRB1)
Jeff Dawson, Risk Assessor (RRB1)
Health Effects Division (7509C)

Mary Waller
Fungicide Branch, Registration Division (7505C)

The Cancer Assessment Review Committee met on October 19, 2005 to evaluate the carcinogenic potential of Iodomethane. Attached please find the Final Cancer Assessment Document.

cc: J. Pletcher
Y. Woo

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF **IODOMETHANE**

(PC Code 000011)

November 10, 2005

CANCER **A**SSESSMENT **R**EVIEW **C**OMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION/
DOCUMENT PREPARATION: Elizabeth Méndez, PhD, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

Karl Baetcke

Lori Brunsman, Statistician

William Burnam, Chair

Marion Copley

Vicki Dellarco

Kit Farwell

Abdallah Khasawinah

Nancy McCarroll

Tim McMahon

Jess Rowland

Linda Taylor

Yin-Tak Woo

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist

OTHER ATTENDEES: Whang Phang (HED/RRB1), Santhini Ramasamy (HED/RRB4), Mike Metzger (HED/RRB1), Felicia Fort (HED/RRB1), Jeff Dawson (HED/RRB1), Alberto Protzel (HED/TB); *via* conference call: Doug Wolf (EPA/ORD/NHEERL/RTP), Lori Lim (CalEPA), Chuck Aldus (CalEPA), Ruby Reed (CalEPA)

TABLE OF CONTENTS

EXECUTIVE SUMMARY

On October 19, 2005 the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Iodomethane.

Dr. Elizabeth Méndez of Reregistration Action Branch I presented chronic toxicity/ carcinogenicity studies in Crl:CD®(SD)IGS BR rats and CD-1 mice by: describing the experimental design; reporting on survival and body weight effects, treatment-related non-neoplastic and neoplastic lesions, statistical analysis of the tumor data, the adequacy of the dose levels tested and presenting the weight of the evidence for the carcinogenicity of Iodomethane. Dr. Méndez also discussed the toxicology, metabolism and structure activity relationships while Dr. Nancy McCarroll presented the mutagenicity data.

In the rat combined chronic toxicity/carcinogenicity study Iodomethane (97.9-99.8% a.i.) was administered to Crl:CD®(SD)IGS BR rats *via* whole body inhalation at concentrations of 0, 5, 20, or 60 ppm for 6 hours/day 5 days/week for 104 weeks. Sixty animals/sex/concentration were exposed to 0, 5, or 20 ppm iodomethane while 70/sex were exposed at the 60 ppm level. In the carcinogenicity study in mice, microencapsulated iodomethane was administered in the diet to groups of 50 male and 50 female Crl:CD®1(ICR) mice at concentrations of 0, 60, 200, or 600 ppm (0, 8, 28, or 84 mg/kg bw/day, respectively, for males and 0, 10, 35, or 100 mg/kg bw/day, respectively, for females) for 18 months.

Also available for consideration were several mechanistic studies used in support of the proposed antithyroidal mode of action (MOA) for the thyroid carcinogenic response observed after iodomethane exposure.

After careful consideration of all the available data, the CARC reached the following conclusions:

Carcinogenicity

Rat

‣ An increased incidence of thyroid follicular cell tumors was observed in male rats exposed to 60 ppm iodomethane *via* the inhalation route. The CARC considered the thyroid follicular tumors (adenoma driven) at the high dose to be treatment-related since there were significant positive trends for all three types (adenomas, $p<0.01$; carcinomas, $p<0.05$; combined adenomas/carcinomas, $p<0.01$), as well as significant differences in the pair-wise comparisons of the 60 ppm dose group with the controls for adenomas (10/42, 24% , $p<0.01$, vs 2/45, 4% controls) and combined adenomas and/or carcinomas, (12/42, 29%, $p<0.05$ vs. 4/45, 9% controls). In addition, the incidences at the high dose exceeded the historical control ranges for adenomas (1.67-12%) and for carcinomas (0.87-3.85%). Females were not affected. Iodomethane only caused a significant increase in thyroid

tumors in male rats as commonly observed in classical antithyroidal agents where male rats are frequently found to be more sensitive to the induction of thyroid follicular cell tumors. In keeping with this, TSH levels are typically higher in male rats than in females.

▸ Dosing at the high dose in male and female rats was considered to be adequate based on increased incidences in both sexes of non-neoplastic lesions in the thyroid, nasal cavity, and salivary glands, decreased body weight (↓18-20%, $p<0.01$) and body weight gains (↓27-28%, $p<0.01$) as well as perturbations of thyroid hormone homeostasis (T_3, T_4, and TSH).

Mice:

▸ At the highest dose tested (600 ppm), male mice exhibited a slight increase (6% *vs* 0 in control) with a positive trend in the combined incidence of thyroid follicular cell tumors (adenomas & carcinomas), exceeding the maximum incidence (2%) observed in historical control data from Charles River Lab (2005) for either tumor type.

– Primarily, the positive trend was driven by the incidence of adenomas (4%) rather than carcinomas (2%).

– This incidence of thyroid tumors is consistent with perturbations of thyroid hormone economy.

▸A slight increase in the incidence of **uterine and cervical fibromas** was observed in female CD-1 mice at 600 ppm. Although significant positive trends for cervical fibromas ($p<0.05$) and combined cervical/uterine fibromas ($p<0.01$) were reported, the lesions were not considered to be treatment-related for the following reasons:

– Microscopic in size

– Occurred only at the terminal sacrifice

– Had no precursor lesions (hyperplasia)

– Not found in the rat bioassay and;

– Fibromas, consisting primarily of collagen fibers, have not been associated with chemical carcinogenicity.

– Moreover, the reproductive tract of female mice of this age occasionally exhibit these types of lesions.

▸ Dosing at the high dose in male and female mice was considered to be adequate for this study based on the increased incidence of non-neoplastic lesions in the thyroid, esophagus, pharynx, stomach, and pituitary, decreased body weights (↓6-11%, $p<0.01$) and body weight gains (↓21-92%, $p<0.01$), as well as changes in serum thyroid/pituitary hormone levels. Thyroid hormone homeostasis was impaired in male mice but not females at the highest dose tested (600 ppm). T_4 was decreased by ≈30% while TSH was increased by ≈91%.

Mutagenicity

Although the guideline mutagenicity studies submitted by the registrant are negative for genotoxicity, there is concern that appropriate measures to prevent compound volatilization may not have been taken. In particular, re-evaluation of the Bacterial Reverse Gene Mutation test (MRID 45593813) indicates that this is not a valid test because the study report did not describe what measures were taken, if any, to keep the test substance "in contact" with the cells.

Numerous studies in the open literature indicate that iodomethane is a methylating agent and consequently a potential mutagen. Evidence of this mutagenic potential is available from numerous *in vitro* assays and one *in vivo* assay (*e.g., S. typhimurium, E. coli,*CHO cells, mouse lymphoma assay, and an *in vivo* DNA adduct formation test).

Although iodomethane has been shown to demonstrate mutagenic potential, it is not considered to operate through a mutagenic mode of action. The majority of the neoplastic lesions observed after iodomethane exposure were benign and were observed at the terminal sacrifice unlike tumors induced through a mutagenic MOA. Another aspect that contradicts a mutagenic MOA is that although DNA adducts are found in multiple organs (*e.g.*, liver, lungs, forestomach) tumors are only seen in the thyroid in the rodent bioassays. This is consistent with the observation that in standard rodent bioassays, no thyroid carcinogen acting by a mutagenic MOA has been identified that does not induce tumors at multiple sites. Finally, the lack of a tumorigenic response at the port-of-entry (respiratory tract) in the Inhalation Combined Chronic/Carcinogenicity study in rats also demonstrates that mutagenicity is not contributing to the carcinogenic profile of iodomethane since tumors in the respiratory tract (particularly the nasal cavity) would be expected if iodomethane were acting through a mutagenic MOA.

Structure-Activity Relationship

Methyl bromide (MeBr), a monohalogenated methane like iodomethane, was considered with regards to its SAR to iodomethane. MeBr was classified as "not likely to be carcinogenic to humans" based on the lack of tumorigenic response in two rodent bioassays in spite of several positive mutagenicity assays. Iodinated glycerol (which contains 3-iodo-1,2-propanediol as its major component), a close structural analog of iodomethane, is an alkyl iodide with alkylating and mutagenic activities and has been shown to induce the same type of thyroid tumors as iodomethane. However, iodinated glycerol is a multi-target carcinogen (including port of entry) whereas iodomethane's carcinogenic effect seems to be confined to the thyroid gland in rodents. In contrast, a number of nongenotoxic iodinated compounds with little or no structural similarity to iodomethane (e.g., amiodarone, potassium iodide) have been shown to elicit similar thyroid carcinogenic effects as iodomethane suggesting that iodide may be the key common link for the thyroid activity.

Mode of Action (MOA)

There is compelling evidence indicating that iodomethane induces thyroid follicular cell tumors through an antithyroidal MOA. Although iodomethane has been shown to be mutagenic primarily in *in vitro* studies and produced DNA adducts in one study in rats, it is not considered to operate through a mutagenic MOA. The weight-of-evidence (WOE) indicates that perturbation of thyroid homeostasis is the key event in the thyroid tumorigenic response observed after iodomethane exposure.

Among the evidence supporting an antithyroidal MOA is the observation that only male rodents exhibit increases in thyroid tumors. This is a common response pattern for classical antithyroidal agents. In addition, the increases of cell growth *in vivo* (*e.g.*, increases in thyroid weights and hyperplasia) progressing to follicular cell tumors were only seen in the presence of thyroid/pituitary hormone changes (decreased T_3 and T_4 in conjunction with profound TSH increases) thus exhibiting a pattern of both dose and temporal concordance. The fact that iodomethane exposure leads to a dramatic increase in serum iodide levels coupled with the changes in thyroid/pituitary hormone levels, thyroid weights, and diffuse follicular cell hyperplasia points to an intrathyroidal site of action further supported by the fact that excess iodide is widely recognized as a goitrogenic agent.

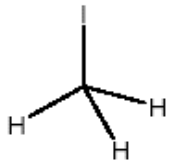
In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), the CARC classified Iodomethane as **"Not likely to be Carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis."** The point of departure for the iodomethane long-term inhalation risk assessment will be based on salivary gland metaplasia, respectively since this endpoint is approximately 7-fold more sensitive than the thyroid hormone effects and thus health protective of any non-cancer adverse outcomes that may be related to perturbations in thyroid hormone homeostasis.

I. INTRODUCTION

On October 19th, 2005 the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Iodomethane.

II. BACKGROUND INFORMATION

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has conducted a preliminary human health risk assessment for the new active ingredient iodomethane, also referred to as methyl iodide or CH3I.



Empirical Formula:	CH_3I
Molecular Weight:	141.95
CAS Registry No.:	74-88-4
PC Code:	000011
Chemical Class:	Alkyl Iodide

The proposed use of iodomethane is as a pre-plant soil fumigant in strawberry, tomato, peppers, and ornamental fields (flowers, plants, and bushes). Iodomethane has been identified as a possible replacement for methyl bromide (MeBr), a fumigant with numerous registered uses. Although iodomethane will be used as an agricultural pesticide, it is considered a non-food use chemical since it is quickly degraded or metabolized into non-toxic degradates and subsequently incorporated into natural plant constituents. Furthermore, iodomethane residues must dissipate in the soil prior to planting to prevent phytotoxicity. Accordingly, HED concludes that tolerances are not required for iodomethane at this time.

The primary exposure pathway for iodomethane is *via* inhalation. The general public may be exposed to iodomethane in air because of its volatility following application. Specifically, fumigants such as iodomethane can off-gas into air and be transported by diffusion and wind off-site. Based on the proposed use patterns, the Agency anticipates exposures would be for short- and intermediate- terms (*i.e.,* ≤ 6 months). In addition, the U.S. population may be exposed to iodomethane through the drinking water.

The pattern of toxicity attributed to iodomethane exposure *via* the inhalation route includes developmental toxicity (manifested as fetal losses and decreased live births), histopathology findings (respiratory tract lesions and salivary gland squamous cell metaplasia), thyroid toxicity, neurotoxicity and generalized systemic toxic effects (body weight and body weight gain decreases).

Since iodomethane is a new active ingredient, it has not been previously reviewed by the CARC. However, the International Agency for Research on Cancer (IARC, 1999) has concluded that iodomethane is "not classifiable as to its carcinogenicity to humans."

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study with Iodomethane in Rats

Reference: A 24-Month Inhalation Combined Chronic Toxicity/Carcinogenicity Study of Iodomethane in Rats. WIL Research Laboratories, LLC, 1407 George Rd., Ashland, OH. Study No. WIL-418019, March 29, 2005. MRID 46512401. Unpublished.

A. Experimental Design

Iodomethane (97.9-99.8% a.i.) was administered to Crl:CD®(SD)IGS BR rats *via* whole body inhalation at concentrations of 0, 5, 20, or 60 ppm for 6 hours/day 5 days/week for 104 weeks. Sixty animals/sex/concentration were exposed to 0, 5, or 20 ppm iodomethane while 70/sex were exposed at the 60 ppm level.

B. Discussion of Tumor Data

Male rats had significant trends for thyroid follicular cell adenomas and adenomas and/or carcinomas combined, both at $p < 0.01$. There was also a significant trend for thyroid follicular cell carcinomas at $p < 0.05$. There were significant differences in the pair-wise comparisons of the 60 ppm dose group with the controls for thyroid follicular cell adenomas at $p < 0.01$ and for thyroid follicular cell adenomas and/or carcinomas combined at $p < 0.05$ (Table 1). The increased incidence of follicular cell adenoma (24%) at 60 ppm was greater than the historical control incidence (2.21%) at the test facility (WIL) and the spontaneous incidence range (1.67- 12.0%) reported by Charles River Laboratories (CRL) for this strain. The increased incidence of follicular cell carcinoma (10%) in 60 ppm males was not statistically significant compared with concurrent controls, however, it was greater than the historical control incidence (0.88%) at the test facility and exceeded the range of spontaneous incidence (0.87-3.85%) reported for this strain by CRL. No treatment-related increase in incidence of neoplasms was observed in female rats at any dose.

Table 1. Male Rats: Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results.

Tumor Type	Exposure Concentration (ppm)			
	0	5	20	60
Adenoma	2/45	2/45	4/49	10[a]/42
%	(4)	(4)	(8)	(24)
p =	0.00065**	0.69179	0.38018	0.00936**
Carcinoma	2/45	0/45	0/49	4[b]/42
%	(4)	(0)	(0)	(10)
p =	0.03136*	1.0000	1.0000	0.30563
Combined	4/45	2/45	4/49	12[c]/42
%	(9)	(4)	(8)	(29)
p =	0.00045**	0.89861	0.68982	0.01745*

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[a]First adenoma observed at week 59, dose 60 ppm.
[b]First carcinoma observed at week 90, dose 60 ppm.
[c]Two animals in the 60 ppm dose group had both an adenoma and a carcinoma.

Note: Interim sacrifice animals have been excluded from this analysis. Three interim sacrifice animals in the 60 ppm dose group had an adenoma.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

C. Non-Neoplastic Lesions

Histopathologic lesions are presented in Tables 2 (interim sacrifice), 3 (thyroid gland, main study), 4 (nasal cavity, main study), and 5 (salivary gland, main study). The incidences of several thyroid gland lesions were increased primarily in 60 ppm males at 52 weeks, and the incidences of nasal cavity and salivary gland lesions were increased in 60 ppm male and female rats at 52 weeks. In the main study, there were treatment-related increases in the incidence and severity of thyroid lesions, seen primarily in 60 ppm males, which is consistent with gross pathology (enlarged thyroid), organ weight (increased weight), and other histopathologic data (increased incidence of neoplastic lesions). There was increased severity and/or incidence of follicular cell hyperplasia, follicular cyst, cytoplasmic vacuolation, follicular-cystic hyperplasia and ultimobranchial cyst. The incidence of follicular cell hyperplasia was also increased in 60 ppm females; increased incidence of ultimobranchial cyst was observed at 20 and 60 ppm in females. Follicular cell hyperplasia is consistent with the elevated levels of TSH in these animals.

Treatment-related changes in the olfactory epithelium along the dorsal aspects of the turbinates and septum, which was evident from epithelium degeneration and the formation of epithelial cysts, were seen in 60 ppm males and females (Table 4). These lesions were found in levels III-VI of the olfactory epithelium. The investigator reported that the overall incidence of olfactory epithelium degeneration was 90% for males and 75% for females after 1 year and 100% for both sexes after 2 years.

Treatment-related effects were also seen in salivary glands in all treatment groups in both sexes (Table 5). An increased incidence of squamous cell metaplasia, primarily at 20 and 60 ppm and atrophy, most extensive at 60 ppm, was observed.

TABLE 2. Non-neoplastic lesions in thyroid from rats exposed to Iodomethane by inhalation – interim study[a]

Organ/lesion	Exposure concentration (ppm)							
	0	**5**	**20**	**60**	**0**	**5**	**20**	**60**
	Males				**Females**			
No. examined	10	10	10	20	10	10[b]	10	20
Thyroid gland								
Follicular cell hyperplasia	0	1	1	8	0	0	0	2
Follicular cyst	0	0	0	3	0	0	0	0
Cytoplasmic. vacuolation	0	1	0	8	0	0	0	0
Follicular cyst hyperplasia	0	0	0	2	0	0	0	0
Ultimobranchial cyst	3	2	4	13	6	4	3	10
Nasal Cavity								
Level III								
Olfactory epithelial degen.	0	0	0	13	0	0	0	1
Olfactory epithelial cyst	0	0	0	11	0	0	0	3
Level IV								
Olfactory epithelial degen.	0	0	0	15	0	1	1	6
Olfactory epithelial cyst	0	0	0	11	0	0	1	10
Level V								
Olfactory epithelial degen.	0	0	1	18	0	0	0	15
Olfactory epithelial cyst	0	0	0	14	0	0	0	15
Level VI								
Olfactory epithelial. degen.	0	0	0	16	0	0	0	8
Olfactory epithelial cyst	0	0	0	5	0	0	0	8
Salivary gland								
Squamous metaplasia.	0	0	3	16	0	0	3	18
Atrophy	0	0	0	8	0	0	0	1

Data obtained from pages 553-596 of MRID 46512401

[a] Values are number of animals

[b] Salivary gland examined in only 9 females at 5 ppm.

Statistical analyses not reported

TABLE 3. Non-neoplastic lesions in thyroid from rats exposed to Iodomethane by inhalation – main study[a]

Severity	Exposure concentration (ppm)							
	0	**5**	**20**	**60**	**0**	**5**	**20**	**60**
	Males				**Females**			
No. examined	50	50	50	50	50	49	50	50
Follicular cell hyperplasia								
Minimal	0	0	0	9	0	1	1	6
Mild	0	1	0	3	0	1	0	3
Moderate	0	0	0	1	0	0	0	1
Total	0	1 (2.00)b	0	13 (1.38)	0	2 (1.50)	1 (1.00)	10 (1.50)
Follicular cyst								
Minimal	0	1	0	0	0	0	0	0
Mild	0	3	3	5	1	2	1	1
Moderate	1	0	1	0	0	0	0	0
Total	1 (3.00)	4 (1.75)	4 (2.25)	5 (2.00)	1 (2.00)	2 (2.00)	1 (2.00)	1 (2.00)
Cytoplasmic vacuolation								
Minimal	0	0	0	5	0	1	0	1
Mild	0	0	0	3	0	0	0	0
Total	0	0	0	8 (1.38)	0	1 (1.00)	0	1 (1.00)
Follicular, cystic hyperplasia								
Minimal	0	1	0	1	0	2	2	0
Mild	1	3	0	4	0	0	0	2
Moderate	0	1	3	1	0	1	0	0
Severe	0	0	1	0	0	0	0	0
Total	1 (2.00)	5 (2.00)	4 (3.25)	6 (2.00)	0	3 (1.67)	2 (1.00)	2 (2.00)
Ultimobranchial cyst								
Minimal	4	6	6	11	7	6	13	11
Mild	2	2	0	2	1	6	7	5
Moderate	0	0	1	2	0	0	0	0
Total	6 (1.33)	8 (1.25)	7 (1.29)	15 (1.40)	8 (1.13)	12 (1.50)	20 (1.35)	16 (1.31)

Data obtained from page 499-544 and 597-632 of MRID 46512401

[a] Values are number of animals

[b] Average severity score for animals with lesions: 1 = minimal, 2 = mild, 3 = moderate, 4 = severe

Statistical analyses not reported

TABLE 4. Non-neoplastic lesions in nasal level III-VI in rats exposed to Iodomethane by inhalation[a]

Severity	Exposure concentration (ppm)							
	0	**5**	**20**	**60**	**0**	**5**	**20**	**60**
	Males				**Females**			
No. examined	50	50	50	50	49	50	50	50
Olfactory epithelium degeneration (level III)								
Minimal	0	0	1	18	0	0	4	16
Mild	0	0	0	5	0	0	0	2
Moderate	0	0	0	5	0	0	0	1
Total	0	0	1 (1.00)	28 (1.54)	0	0	4 (1.00)	19 (1.21)
Olfactory epithelium cyst (level III)								
Minimal	0	0	0	5	0	0	0	5
Mild	0	1	0	0	0	0	0	1
Total	0	1 (2.00)	0	5 (1.00)	0	0	0	6 (1.17)
Olfactory epithelium degeneration (level IV)								
Minimal	0	2	4	22	0	0	2	20
Mild	0	0	0	14	0	0	1	9
Moderate	0	0	0	7	0	0	0	7
Severe	0	0	0	1	0	0	0	1
Total	0	2 (1.00)	4 (1.00)	44 (1.70)	0	0	3 (1.33)	37 (1.70)
Olfactory epithelium cyst (level IV)								
Minimal	0	0	0	10	1	0	0	8
Mild	0	0	0	0	0	0	0	0
Total	0	0	0	10 (1.00)	1 (1.00)	0	0	8 (1.00)
Olfactory epithelium degeneration (level V)								
Minimal	0	1	3	17	0	0	3	17
Mild	0	0	0	18	0	0	1	18
Moderate	0	0	0	7	0	0	0	6
Severe	0	0	0	3	0	0	0	4
Total	0	1 (1.00)	3 (1.00)	45 (1.91)	0	0	4 (1.25)	45 (1.93)
Olfactory epithelium cyst (level V)								
Minimal	0	0	0	17	0	0	1	20
Mild	0	0	0	4	0	0	0	0
Total	0	0	0	21 (1.19)	0	0	1 (1.00)	20 (1.00)
Olfactory epithelium degeneration (level VI)								
Minimal	1	0	2	7	0	0	1	17
Mild	0	0	1	21	0	0	1	17
Moderate	0	0	0	8	0	0	0	7
Severe	0	0	0	2	0	0	0	2
Total	1 (1.00)	0	3 (1.33)	38 (2.13)	0	0	2 (1.50)	43 (1.86)
Olfactory epithelium cyst (level VI)								
Minimal	0	0	0	13	0	0	0	20
Mild	0	0	0	1	0	0	0	0
Total	0	0	0	14 (1.07)	0	0	0	20 (1.00)

Data obtained from pages 499-544 and 597-632 of MRID 46512401

[a] Values are number of animals

Statistical analyses not reported

TABLE 5. Non-neoplastic lesions in salivary glands from rats exposed to Iodomethane by inhalation[a]

Severity	Exposure concentration (ppm)							
	0	5	20	60	0	5	20	60
	Males				Females			
No. examined	50	49	49	50	50	50	50	50
Squamous metaplasia								
Minimal	1	3	20	22	0	1	16	29
Mild	0	1	2	25	0	2	6	9
Moderate	0	0	0	0	0	0	0	2
Total	1 (1.00)	4 (1.25)	22 (1.09)	47 (1.53)	0	3 (1.67)	22 (1.27)	40 (1.33)
Atrophy								
Minimal	0	2	2	11	0	2	2	8
Mild	0	3	2	3	0	0	3	1
Moderate	0	0	0	0	0	0	0	0
Total	0	5 (1.60)	4 (1.50)	14 (1.40)	0	2 (1.00)	5 (1.60)	9 (1.11)

Data obtained from pages 499-544 and 597-632 of MRID 46512401
[a] Values are number of animals
Statistical analyses not reported

D. Adequacy of the Dosing for Assessment of Carcinogenicity

Though survival was low (34-38% for control and 60 ppm males and females, 46-48% for the other groups), it did not appear to be affected by exposure to the test article since the high-dose and control groups had comparable mortality rates. In addition to the histopathology findings described above, iodomethane exposure led to decreases in body weight(↓18-20%) and body weight gains (↓27-28%) in both sexes. Iodomethane exposure at a concentration of 60 ppm also elicited significant perturbations of thyroid hormone homeostasis as evidenced by the decreases in T_3 serum levels (↓11-34%) and the sustained increases in TSH and rT_3 (↑305-1141% and 111-133%, respectively). Interestingly, changes in T_4 serum levels were inconsistent decreasing by 56% on week 26, increasing by 34% on week 52, and being comparable to control during the week 104 evaluation. A similar pattern of effects was noted in females at the highest concentration tested. However, in general, the magnitude of the changes in serum hormone levels was not as robust as in the case of males (T_3:↓11-27%, TSH:↑58-634%, rT_3: ↑90-380%) particularly for TSH. The CARC considered dosing at the high dose in both sexes to be adequate for the assessment of carcinogenicity of iodomethane.

2. Carcinogenicity Study in Mice

Reference: An 18 month dietary carcinogenicity study of miroencapsulated iodomethane in mice. WIL Research Laboratories, LLC, 1407 George Road, Ashland, OH 44805, Project ID. WIL-418025. June 24, 2005. MRID 46582801. Unpublished.

A Pathology Working Group (PWG) Peer Review of proliferative lesions reported in the uterus and cervix. Supplemental to Vol. 118: An 18-month carcinogenicity study of microencapsulated iodomethane in female CD-1 mice. Experimental Pathology Laboratories, Inc., P.O. Box 12766, Research Triangle Park, NC 27709, Project ID No. 758-011. June 23, 2005. MRID 46582802. Unpublished

A. Experimental Design

Microencapsulated iodomethane (batch/lot #: 20-379, 20-380, 20-386, 20-728, 20-430, 20-442, 20-443, 20-454, 20-456, 20-481, 20-483, 20-490, 20-496, 20-500, 20-517, 20-525, 20-528) was administered in the diet to groups of 50 male and 50 female Crl:CD®1(ICR) mice at concentrations of 0, 60, 200, or 600 ppm (0, 8, 28, or 84 mg/kg bw/day, respectively, for males and 0, 10, 35, or 100 mg/kg bw/day, respectively, for females) for 18 months.

B. Discussion of Tumor Data

As shown in Table 6, an increase in the incidence of thyroid follicular cell adenoma/carcinoma combined in high-dose male mice was noted; the incidence was 0%, 0%, 2%, and 6% in the control, low-, mid-, and high-dose groups, respectively. Follicular cell adenoma in mice are rare and occurred in none of the historical controls from the performing laboratory.

In the case of the increased incidence of fibromas seen in the uterus and cervix, two PWGs were convened to further evaluate the female reproductive tract findings (Drs. Marion Copley and John Pletcher attended these meetings). The reviews consisted of re-examination of all sections of the ovary, uterus, and cervix containing lesions initially diagnosed as histiocytic sarcoma as well as other proliferative mesenchymal lesions in the uterus and/or cervix, and re-examination of lesions in which a different diagnosis was presented by the study pathologist and reviewing pathologists. Additional sections from wet tissues and paraffin blocks were examined after staining with hematoxylin, eosin, and PAS to investigate proliferative granular cell lesions. Sections were stained immunohistochemically for S100 protein, Actin, and Desmin and histochemically with a Trichrome stain to identify collagen and muscle fibers in tissues. The PWG also re-examined lesions diagnosed as granular cell tumors, leiomyoma, leiomyosarcoma, and endometrial stromal sarcoma. The lesions were classified according to the criteria and nomenclature approved by the Society of Toxicologic Pathology (STP) and the International Agency on Research in Cancer (IARC). The PWGs concluded that the lesions evaluated were not treatment related since they occurred only in animals sacrificed at study termination, were microscopic in size, had no

precursor lesion (hyperplasia), and were not found in rats treated with iodomethane for 2 years. The slight increase in benign fibrous tumors (fibromas) in the uterus/cervix of the 600 ppm females was considered incidental. Such tumors, consisting primarily of collagen fibers, have not been associated with chemical carcinogenicity. In Table 7, there were statistically significant trends for cervix adenomas ($p<0.05$) and combined cervix adenomas and uterine fibromas ($p<0.01$). No statistically significant pair-wise comparisons with controls were noted.

Table 6. Male Thyroid Follicular Cell Tumor Rates[+] and ad hoc Fisher's Exact Test and Exact Test for Trend Test Results

Tumor Type	Dose (mg/kg/day)			
	0	8	28	84
Adenomas	0/50	0/50	1/50	2/49
%	(0)	(0)	(2)	(4)
p =	0.05969	1.00000	0.50000	0.24242
Carcinomas	0/50	0/50	1/50	1/49
%	(0)	(0)	(2)	(2)
p =	0.1841	1.00000	0.50000	0.49495
Combined	0/50	0/50	1/50	3/49
%	(0)	(0)	(2)	(6)
p =	0.01787*	1.00000	0.50000	0.11746

+Number of tumor bearing animals/Number of animals examined.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 7. Female Cervix and Uterine Tumor Rates[+] and ad hoc Fisher's Exact Test and Exact Test for Trend Test Results

Tumor Type	Dose (mg/kg/day)			
	0	10	35	100
Cervix Fibromas	0/49	1/50	0/47	3/50
%	(0)	(2)	(0)	(6)
p =	0.03575*	0.50505	1.00000	0.12496
Uterine Fibromas	0/50	1/50	0/50	1/50
%	(0)	(2)	(0)	(2)
p =	0.3128	0.50000	1.00000	0.50000
Combined	0/50	1/50	0/50	4/50
%	(0)	(2)	(0)	(8)
p =	0.00992**	0.50000	1.00000	0.05873

+Number of tumor bearing animals/Number of animals examined.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

C. Non-Neoplastic Lesions

Notable non-neoplastic lesions are presented in Table 8. Administration of iodomethane primarily affected the thyroid gland, pharynx, esophagus, and nonglandular stomach, in both sexes. The incidence of hyperkeratosis in the esophagus, pharynx, and stomach was significantly increased in both sexes at doses $\geq$200 ppm, females in the 60 ppm group also exhibited a statistically significant increase in the incidence of hyperkeratosis in the esophagus. Hyperkeratosis in the esophagus, pharynx, and nonglandular stomach was seen in 23-64% of mid-dose males, 33-68% of mid-dose females, 53-78% of high-dose males, and 62-90% of high-dose females. Incidences were 1-10%, control males and 0-38% in control females. The incidence of hyperkeratosis in the esophagus of low-dose females was 10%. The incidences of epithelial hyperplasia in the esophagus in high-dose male mice and hyperkeratosis in the pharynx in low-dose female mice were increased but not significantly compared with control incidences. The severity of the lesions in the esophagus, pharynx, and stomach did not show a clear dose-related trend in either sex. The incidence of basophil hypertrophy in the pituitary was significantly increased at all doses in females (61-70%). The severity of the lesion was minimal in almost all animals. The incidence of basophil hypertrophy showed no clear dose-related trend.

The thyroid gland was the primary target of iodomethane in male and female mice. Both sexes had significantly increased incidences of cytoplasmic vacuolation of follicular epithelial cells (24-44% in males and 24-30% in females *vs* 0 control) and increased colloid in the follicular epithelial cells (56-88% in males and 62-72% in females) at all dose levels compared with control incidences of

0% for cytoplasmic vacuolation and 6% and 16% for increased colloid in control males and females, respectively. Female mice at all dose levels and high-dose male mice had a significantly increased incidence of follicular cell hyperplasia (44-52% in females and 12% in males compared with 0-2% in controls). The incidence of hyperplasia of follicular epithelial cells (referred to as hyperplasia) was significantly increased in high-dose male mice as well as in mid- and high-dose females, (not statistically significant). Increased colloid and follicular cell hyperplasia in male mice were the only thyroid gland lesions that showed clear dose-related trends; nevertheless, all the thyroid gland lesions are considered treatment related. The severity of the lesions was generally increased in treated mice compared with controls, but no clear dose-related trend was observed.

TABLE 8. Microscopic lesions in male and female mice receiving microencapsulated iodomethane for 78 weeks

Organ/lesion	Dietary concentration (ppm)			
	0	60	200	600
Males				
Esophagus [No. examined]	[50]	[50]	[50]	[49]
Hyperkeratosis	3 (1.00)[a]	4 (1.25)	28** (1.11)	38** (1.18)
Epithelial hyperplasia	0	0	0	4 (1.00)
Pharynx [No. examined]	[50]	[50]	[48]	[49]
Hyperkeratosis	1 (2.00)	3 (1.00)	11** (1.00)	26** (1.08)
Stomach, nonglandular [No. examined]	[49]	[50]	[50]	[49]
Hyperkeratosis	5 (1.00)	11 (1.09)	32** (1.06)	38** (1.16)
Thyroid gland [No. examined]	[50]	[50]	[50]	[49]
Cytoplasmic vacuolation	0	12** (1.25)	22** (1.09)	15** (1.13)
Increased colloid	3 (1.00)	28** (1.43)	37** (1.38)	44** (1.48)
Hyperplasia of follicular epithelial cells	0	4 (1.50)	2 (1.50)	8** (1.13)
Follicular cell hyperplasia	0	1 (1.00)	3 (1.00)	6* (1.00)
Females				
Esophagus [No. examined]	[50]	[50]	[50]	[50]
Hyperkeratosis	0	5* (1.00)	27** (1.00)	45** (1.13)
Pharynx [No. examined]	[49]	[50]	[49]	[50]
Hyperkeratosis	1 (1.00)	5 (1.00)	16** (1.06)	31** (1.16)
Pituitary [No. examined]	[48]	[49]	[49]	[50]
Basophil hypertrophy	13 (1.15)	30** (1.00)	28** (1.00)	35** (1.03)
Stomach, nonglandular [No. examined]	[50]	[50]	[50]	[50]
Hyperkeratosis	19 (1.11)	20 (1.15)	34** (1.06)	36** (1.14)

TABLE 8. Microscopic lesions in male and female mice receiving microencapsulated iodomethane for 78 weeks

Organ/lesion	Dietary concentration (ppm)			
	0	60	200	600
Thyroid gland [No. examined]	[50]	[50]	[50]	[50]
Cytoplasmic vacuolation	0	15** (1.00)	14** (1.21)	12** (1.08)
Increased colloid	8 (1.13)	35** (1.17)	31** (1.29)	36** (1.33)
Hyperplasia of follicular epithelial cells	1 (1.00)	2 (1.50)	5 (1.00)	5 (1.00)
Follicular cell hyperplasia	1 (1.00)	25** (1.28)	22** (1.27)	26** (1.19)

Data taken from Tables 55 (pp. 445-484) and 57 (pp. 489-531), MRID 46582801.
[a]average severity of the animals with lesions, calculated by the reviewer: 1 = minimal, 2 = mild, 3 = moderate.
*p≤0.05, **p≤0.01, statistically significant

D. Adequacy of Dosing for Assessment of Carcinogenicity

Dosing was considered adequate for this study based on decreased body weight (↓6-11%, p< 0.01) and weight gain (↓21-92%, p<0.01), induction of non-neoplastic lesions in the thyroid, pharynx, esophagus, stomach, and pituitary gland, as well as the changes in serum hormone levels (TSH and T4).

IV. TOXICOLOGY

1. Metabolism

A rat metabolism study comparing absorption after oral and inhalation administration is available. Sprague-Dawley rats were orally dosed or exposed via inhalation with [^{14}C] CH_3I. Maximum blood concentrations were achieved within 4 hours (oral) and 0-2 hours (inhalation), and were proportional to dose/concentration. Initial $t_{½}$ was 5.1-7.2 hours, and terminal $t_{½}$ was 116-136 hours. Radioactivity recovery was low in the main test due to inefficient CO_2 trapping. Overall recovery in the supplementary test was increased due to increased recovery of carbon dioxide. Recovered radioactivity was primarily as CO_2 (39.40-60.81% dose) and in the urine (26.50-33.40% dose) in all treated groups, while feces accounted for <2% dose. Radioactivity remained in the carcasses (11.92-14.39% dose) of all treated animals 168 hours following treatment in the main test. Elimination $t_{½}$ were 17.8-22.3 hours for urine and 29.7-38.0 hours for feces in all treatment groups of the main test. The elimination $t_{½}$ was 5.8-6.8 hours for CO_2 in all treatment groups of the supplementary test. These half-lives, however, are measured on the basis of the ^{14}C radiolabel and may not accurately reflect the amount of iodomethane or iodide remaining in the body since the methyl and iodide moieties of iodomethane are expected to quickly dissociate after administration.

At 0-1 hour post-treatment in orally treated rats and 233 ppm inhalation exposed rats, relatively high levels of radioactivity were observed in the liver and GI tract. Radioactivity was relatively high in the kidney, lung, and nasal turbinates of the 25 ppm inhalation exposed rats and in the kidney, thyroid, and lung of the 233 ppm inhalation exposed rats. At 6 hours post-oral dosing, tissue concentrations increased in the spleen (at 1.5 mg/kg only), kidney, brain, thyroid, lung, nasal turbinates, and fat (at 1.5 mg/kg only). Tissue concentrations decreased in all tissues of the inhalation exposed rats at 6 hours after exposure. At 168 hours post-dose, radioactivity had declined in all tissues and was highest in the kidney, liver, and thyroid. The data in this study indicate that iodomethane is quickly absorbed through both routes of exposure (maximum blood concentration at 2-4 hours). In contrast, the elimination profile indicates that excretion of ^{14}C-labeled iodomethane is biphasic with the initial half-life of 5-7 hours and a terminal half-life of approximately 116-136 hours. Radioactivity accumulates in a variety of tissues including the thyroid (radioactivity concentration of 106-198 μg/g tissue).

Since inorganic iodide levels in the serum have been implicated in the MOA proposed by the registrant for both the rabbit fetal losses and the rat thyroid tumorigenesis, serum inorganic iodide concentrations were measured in several studies including a 2 Day Inhalation Toxicity Study in rats exposed to 0, 25, or 100 ppm iodomethane for 6 hours/day. Serum sample in this study were collected at 0, 1, 3, 6, 9, 24, 25, 27, 30, 33 , and 48 hours. Inorganic iodide increased dramatically during the exposure period at the 25 and 100 ppm concentrations (↑≈300-1400X and 1300-3500X, respectively). Forty eight hours after iodomethane exposure inorganic iodide serum concentrations were still 53X and 321X higher than controls. In general, serum iodide concentrations exhibited a biphasic pattern with peaks occurring at approximately 3-9 hours and at 30-33 hours of exposure. A similar pattern of iodide disposition was observed in a MOA study in rabbits designed to further characterize the fetal losses seen in various Developmental Toxicity Studies in rabbits. Additional information on these experiments is provided on the Mode of Action section of this document.

Also available is a series of *in vitro* studies designed to determine partition coefficients for rat and rabbit tissues, rabbit fetal and maternal blood, and human blood. Overall, the partition coefficients for rat and rabbit tissues (brain, fat, kidney, muscle, and nasal tissue) were similar. Some species-dependent variability in partition coefficients was detected. Specifically, the partition coefficient for rabbit thyroid gland tissue was 3-fold greater than that for rats (39:11) and the partition coefficient for rat liver tissue was 2-fold greater (24:13) than that for rabbit. The partition coefficients for rat, rabbit and human blood were 39, 16, and 18, respectively. Partition coefficients for male and female human blood were similar and partition coefficients for rabbit maternal and fetal blood were similar (12:16). These data were collected to provide critical information for the development of a computational fluid dynamics PB-PK model for use in risk assessment for iodomethane.

2. Mutagenicity

With the exception of a positive finding in the *In Vitro* Chromosomal Aberration in Chinese Hamster Ovary Assay, all guideline mutagenicity studies submitted by the registrant were negative for mutagenicity. However, there are numerous reports in the peer-reviewed literature that indicate methyl iodide is mutagenic in a variety of *in vitro* and *in vivo* assays. Given that iodomethane is highly volatile, it is possible that the guideline studies were negative because the compound was not "in contact" with the cells for a sufficient period of time to cause its mutagenic effect.

(i) In an Ames assay, when tested in Salmonella *typhimurium* strains TA98, TA100, TA1535, and TA1537; and in *Escherichi coli* at concentrations ranging from 0.015-5000 µg/plate iodomethane was non mutagenic with or without metabolic activation (MRID No. 45593813).

(ii) In an *In vitro* Chromosomal Aberrations in Chinese Hamster Ovary Cells Assay, iodomethane was positive for structural chromosome aberrations (clastogenesis) but negative for induction of numerical aberrations at exposures concentrations ranging from 25-350 µg/mL (MRID No. 45593815).

(iii) In an *In Vitro* Mammalian Cell Mutation Test in Chinese Hamster Ovary Cells, iodomethane was negative for increases in mutant colonies (with or without metabolic activation) at exposure concentrations ranging from 100-600 µg/mL (MRID 45593815).

(iv) In a micronucleus test, no increases in micronuclei was seen following a single intraperitoneal injection at doses of 25, 50, or 100 mg/kg (MRID No. 45593816).

(v) Several 005366 studies are available in the peer reviewed literature (see Review of Iodomethane Mutagenicity Studies, TXR 0053665). In general, these studies provide compelling evidence of the mutagenic potential of iodomethane.

– Based on a revisit of the mutagenicity studies submitted by the Registrant and an independent assessment of the data from the open literature, HED concludes that:

- Due to the volatility of CH_3I at 42°C, the bacterial reverse gene mutation test (OPPTS 870.5100 (§84-2)]) submitted by the Registrant (MRID 45593813) is not a valid study and is **unacceptable** because the provisions claimed by TSG were not included in the Final Report and, therefore, could not be verified.

- There is convincing evidence that CH_3I is mutagenic in somatic cells (producing multiple effects, such as gene mutations and chromosomal aberrations) from a diverse range of phylogenetically distinct species such as bacteria, yeast, and mammalian cells but only if steps are taken to contain the test substance (*e.g.*, performing the assay in a desiccator, performing the assay on cultures in suspension, or using sealed petri dishes; if a filter disc

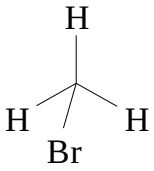
is used, it must be impregnated and placed on top of the agar).

- There is convincing evidence that CH_3I is DNA reactive, binds to, or damages DNA from multiple test systems including DNA damage in bacteria, *in vitro* and *in vivo* DNA adduct formation.

- There are positive results from at least one whole animal genetic toxicology assay (*i.e*, DNA adduct formation in the liver, lung, stomach and forestomach of male and female F344 rats exposed either via the oral or inhalation routes) which suggests that CH_3I has a systemic genotoxic effect.

3. Structure-Activity Relationship

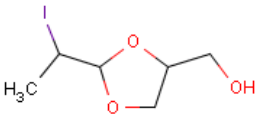
Methyl bromide has been classified as "not likely to be carcinogenic to humans" based on the lack of carcinogenic response in the Combined Chronic/Carcinogenicity Study in rats and the Carcinogenicity Study in Mice although there was evidence of mutagenicity in several guideline mutagenicity studies.



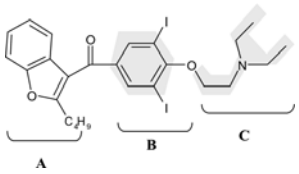
CAS No. 74-83-9

Methyl chloride has been classified by the Agency as well as the International Agency for Research on Cancer (IARC) "not classifiable as to its human carcinogenicity." However, weak to moderate mutagenicity has been demonstrated in *S. typhimurium* (albeit at high concentrations), and an increased incidence of tumor formation (benign and malignant) in B3C6F1 male mouse kidneys at doses of 225 and 1000 ppm does provide some suggestive information of carcinogenic risk, although no renal tumors were found in female mice or in either sex of rats tested in the same study.

Iodinated glycerol (which contains 3-iodo-1,2-propanediol as its major component), a close structural analog of iodomethane, is also an alkyl iodide with alkylating and mutagenic activities and has been shown to induce the same type of thyroid tumors as iodomethane. However, iodinated glycerol is a multi-target carcinogen (including port of entry) whereas iodomethane's carcinogenic effect seems to be confined to the thyroid gland in rodents. In contrast, a number of **nongenotoxic iodinated compounds** with little or no structural similarity to iodomethane (e.g., amiodarone, potassium iodide) have been shown to elicit similar thyroid carcinogenic effects as iodomethane suggesting that iodide may be the key common link for the thyroid activity.



Iodinated glycerol



Amiodarone

4. Subchronic and Chronic Toxicity

a) Subchronic Toxicity

In a subchronic inhalation toxicity study (MRID 45593810), rats were dynamically exposed to iodomethane vapor for 6 hours/day, 5 days/week for 13 weeks at analytical concentrations of 0, 5, 21, or 70 ppm (0, 0.029, 0.12, or 0.41 mg/L/day). There were no effects on mortality, ophthalmology, urinalysis, hematology, organ weights, or gross pathology. The NOAEL is 21 ppm (0.12 mg/L/day), and the LOAEL is 70 ppm (0.41 mg/L/day) based on initial decreases in body weights, body weight gains, and food consumption (males); and nasal degeneration. Respiratory irritation was observed at the interim (4 weeks) and terminal sacrifices. Microscopic findings indicated minimal to mild degeneration/regeneration of the nasal tissues characterized by subacute inflammation, respiratory epithelial metaplasia, degeneration, goblet cell hypertrophy, squamous cell hyperplasia, and minimal alveolar macrophages (females only). Notably, no effects on thyroid histopathology were observed during this study (thyroid hormone levels were not measured).

b) Chronic Toxicity

A Chronic Toxicity Study in dogs is not available for iodomethane. Thus the only studies that evaluate the potential impact of chronic exposure to iodomethane are the Inhalation Combined Chronic Toxicity/Carcinogenicity in Rats and the Dietary Carcinogenicity Study in Mice. The executive summaries on non-neoplastic findings for these two studies follow:

(i) EXECUTIVE SUMMARY for Chronic Toxicity in Rats: Details are discussed in Section III.

The systemic LOAEL for iodomethane in rats is 20 ppm based on increased incidence of salivary gland squamous cell metaplasia. The NOAEL is 5 ppm. The port-of-entry LOAEL is 60 ppm based on increased incidence of olfactory epithelium degeneration and cysts. The NOAEL is 20 ppm.

(ii) EXECUTIVE SUMMARY for Carcinogenicity Study in Mice: Details are discussed in section III.

The LOAEL for microencapsulated iodomethane in mice is 60 ppm (8 and 10 mg/kg bw/day for males and females, respectively) based on histopathologic findings in the thyroid gland (cytoplasmic vacuolation and increased colloid) in both sexes, and hyperkeratosis in the esophagus of females. The NOAEL was not established.

c) Open Literature

In addition to the guideline studies, the committee discussed two rodent bioassays from the open literature. In the first study, strain A mice were exposed once weekly to 0, 0.06, 0.15, or 0.31 nmoles/kg mouse of iodomethane *via* intraperitoneal injection (an exposure pathway not relevant for the iodomethane risk assessment) for 24 weeks. A slight increase in the average number of lung tumors/mice was reported at the highest dose tested (0.55 *vs* 0.28). It is important to note, however, that this is a multiplicity model rather than an incidence model since the strain is prone to developing lung tumors in the absence of any carcinogen. Shimkin and Stoner - developers of this assay - have set forth criteria for interpretation of lung tumor data in the strain A mouse. The first criterion is that lung tumor multiplicity must be statistically significant higher than in control and preferably higher than 1.[1] In the case of iodomethane, the increased incidence was statistically significant at the 0.05 level but was not higher than 1. Thus under the conditions of this assay, iodomethane may be classified as a weak carcinogen. In the second study obtained from the literature, 535-DB strain rats received a weekly dose of 10 or 20 mg/kg iodomethane *via* subcutaneous injection (an exposure pathway not relevant for the iodomethane risk assessment). These rats developed local sarcomas which occasionally metastasized into the lungs and lymph nodes. However, the study had to be terminated earlier than expected since necrosis frequently occurred at the injection site. It is important to note that when the compound was administered *via* the oral route or intravenous injections no tumors developed. Thus it appears that the carcinogenic response is weak given the induction time needed to elicit the tumorigenic response and limited to the port-of-entry.

5. Mode of Action Studies

Though mechanistic studies specifically designed to elucidate the mode of action (MOA) leading to thyroid tumorigenesis are not available, there are numerous studies that indicate perturbation of thyroid hormone homeostasis is a critical effect of iodomethane exposure. Alterations in serum T_3, T_4, and TSH levels have been seen in several studies in rats, mice, and rabbits.

The registrant, Arysta, has proposed perturbations of thyroid hormone homeostasis as the MOA operative in the thyroid tumorigenic response to iodomethane exposure, implicating the elevated serum levels of inorganic iodide as a critical element in the proposed MOA. Iodide excess inhibits the iodination of thyroglobulin in the thyroid gland as well as the release of T_4 and T_3 from the gland.[2] Both effects could lead to an increase in TSH levels. If sustained, this increase in TSH levels can result in thyroid cell hypertrophy, hyperplasia, and eventually tumor formation. Consequently, excess iodide has been linked to the development of antithyroidal activity and

[1] Poirier, LA *et al.*, (1975) "Bioassay of Alkyl Halides and Nucleotide Base Analogs by Pulmonary Tumor Response in Strain A Mice" *Cancer Res.* **35:**1411-1415

[2] Pisarev MA, Gartner R (2000). *Autoregulatory actions of iodine.* In: Braverman LE, Utiger RD eds. Werner and Ingbar's the thyroid: A fundamental and clinical text. Pp 85-90

thyroid tumor formation.[3]

After iodomethane exposures, dramatic increases in inorganic iodide serum levels in conjunction with changes in thyroid/pituitary hormone serum levels have been detected in the rat (Tables 9a & b) as well as the rabbit (Tables 10a-d).[4] Similar to the pattern of thyroid/pituitary hormone seen in rats and rabbits, mice also exhibited hormonal perturbations though no measures of serum iodide levels are available for this species (Table 11).[5] It is noteworthy that thyroid follicular cell tumors in mice and rats are only seen at doses eliciting substantial sustained increases in TSH serum levels in rats and mice (↑>300 and 91%, respectively).

Data used to demonstrate that an antithyroidal activity MOA is operative include increases in cellular growth, hormone changes, site of action information, dose correlations, reversibility, lesion progression, and structure activity relationships. With the exception of reversibility, the iodomethane database contains information on all these elements of the MOA. Evidence of increased cellular growth are available in the Combined Chronic Toxicity/Carcinogenicity Study in rats, Carcinogenicity Study in mice, and the MOA for fetotoxicity study in rabbits.

In the Combined Chronic Toxicity/Carcinogenicity Study in rats, increases in both absolute and relative (to body weight) thyroid/parathyroid weights (↑83-197% and 110-229%, respectively) and increases in the incidence of follicular cell hyperplasia (30% *vs* 0% control) were observed in male rats exposed at the dose level (60 ppm) where thyroid tumors were seen. Moreover, T_3 serum hormone levels were reduced by ≈11-34% while TSH was increased by ≈300-1100% (changes in T_4 levels were inconsistent throughout the study) [Table 9b]. No thyroid tumors were seen at dose levels that failed to cause increases in thyroid/parathyroid weights, follicular cell hyperplasia, and sustained thyroid/pituitary hormone perturbations. In terms of the site of action, given the essential role of iodine in the proper function of the thyroid gland (both iodine deficiency and excess can have profound effects on thyroid function and thyroid hormone biosynthesis) and the fact that iodomethane exposure leads to an excess accumulation of iodine in the thyroid, it appears that the proposed MOA for iodomethane's thyroid tumorigenic response is mediated by an intrathyroidal site of action [Tables 9a and 10a&b]. Progression of lesions was also demonstrated in this study. An increased incidence of thyroid follicular cell hyperplasia but not neoplastic lesions was evident at the interim histopathological examination (week 52) while both hyperplasia

[3] USEPA (1998) *Assessment of Thyroid Follicular Cell Tumors* Office of Research and Development, Risk Assessment Forum; EPA report no.EPA/630/R-97/002

[4] "Mode of Action Study for Iodomethane-Related Fetotoxicity in Rabbits" (MRID 46451002), "Iodide in rat serum by ion chromatography study" and "A 24-Month Inhalation Combined Chronic Toxicity/Carcinogenicity Study of Iodomethane in Rats." (MRID 46512401)

[5] "An 18 month dietary carcinogenicity study of miroencapsulated iodomethane in mice."(MRID 46582801)

and neoplastic lesions were observed at the end of the study (week 104).

In the Carcinogenicity Study in mice, increases in the absolute and relative (to body) thyroid weights were reported for males at all dose levels (↑133-138% and 152-157%, respectively)in conjunction with an increased incidence of follicular cell hyperplasia at the highest dose tested only (12% *vs*. 0 in control). Interestingly, though thyroid/parathyroid weights and follicular cell hyperplasia incidences were increased at all dose levels in females, no progression to follicular cell adenomas and/or carcinomas was seen for females while males exhibited a tumorigenic response (albeit weak). A dose-related increase in TSH (↑53-91%) was reported for males but not females accompanied by a slight reduction in T_4 ($\downarrow \leq 30\%$).

Changes in hormone levels were also noted in the MOA study for iodomethane-related fetotoxicity in rabbits. When animals were exposed to 20 ppm iodomethane for 4 days, maternal TSH levels were increased by 29-56%, T_3 was decreased 11-23%, and T_4 was decreased 20-71%. Fetal TSH was unaffected by maternal exposure to iodomethane but T_3 was decreased (↓19-29%). Histopathology evaluation revealed an increase in the incidence of follicular cell hypertrophy in dams (40% *vs* 0 controls) and fetuses (100% *vs* 0 control) after 4 days of exposure. Interestingly, the fetal incidence of follicular cell hypertrophy after a 4 day recovery period was 54%. Since exposure to iodomethane in this study was only for four days, no data are available to ascertain what the impact of prolonged exposure would have been on the rabbit thyroid. However, the effects seen after such a brief exposure does provide some insight into the overall pattern of thyroid toxicity seen after iodomethane exposure.

Though there are abundant data suggesting that iodomethane induces thyroid follicular cell tumors through an antithyroidal MOA, the fact that iodomethane has been shown to have mutagenic properties precludes the exclusion, at this time, of mutagenicity as a contributing factor in thyroid tumorigenesis. However, if mutagenicity was contributing to tumorigenesis, portal-of-entry (respiratory tract) tumors would be expected.

TABLE 9a. Serum iodide (inorganic) in rats following inhalation exposure to iodomethane:

Exposure group (ppm)	Collection time (hrs)	Inorganic iodide (ng/ml)[a]
0	0	17[b]
	1	17[b]
	3	19[b]
	6	22[b]
	9	39[b]
	24	19[b]
	25	14[b]
	27	14[b]
	30	4.1[b]
	33	13[b]
	48	14[b]
25	1	5070±721
	3	9510±3800
	6	25,600±1940
	9	18,400±1550
	24	1260±83.9
	25	5960±576
	27	10,800±1100
	30	34,100±8170
	33	24,700±1310
	48	742±141
100	1	22,900±1620
	3	60,300±2860
	6	53,800±4480
	9	52,500±8230
	24	8170±1850
	25	27,200±13,700
	27	55,200±3050
	30	83,200±7840
	33	58,300±6520
	48	4500±396

[a] Mean ± SD of 3 rats

[b] estimate at or below limit of quantitation; overall mean±SD for control (0 ppm) group was 17±9 ng/ml

Data taken from Table V, p. 23, Exygen Study No. P0000882

TABLE 9b. Changes in serum thyroid hormone levels in rats exposed to Iodomethane by inhalation[a]

Parameter	Exposure concentration (ppm)							
	0	5	20	60	0	5	20	60
	Males				Females			
Week 26								
T3 (ng/dL)	57.50 ± 5.80	51.40 ± 18.63	57.12 ± 21.19	38.08 ± 16.27 (66)[b]	67.54 ± 28.27	55.38 ± 17.05	80.12 ± 21.93	49.44 ± 19.65 (73)
T4 (µg/dL)	3.87 ± 0.99	3.38 ± 0.44	3.24 ± 0.47	1.71 ± 1.41** (44)	2.03 ± 0.59	1.68 ± 0.57	1.93 ± 0.51	1.78 ± 0.65 (88)
TSH (ng/mL)	2.46 ± 1.23	3.78 ± 1.86	4.92 ± 3.87	30.53 ± 13.69** (1241)	1.76 ± 0.62	1.76 ± 0.54	2.09 ± 0.66	12.92 ± 13.36** (734)
rT3 (ng/mL)	0.13 ± 0.05	0.12 ± 0.05	0.11 ± 0.05	0.15 ± 0.03	0.10 ± 0.05	0.11 ± 0.03	0.15 ± 0.05	0.19 ± 0.09 (190)
Week 52								
T3 (ng/dL)	43.23 ± 11.36	38.95 ± 15.64	51.34 ± 40.35	38.29 ± 11.37 (89)	81.78 ± 33.13	78.70 ± 20.46	60.10 ± 9.84	72.55 ± 15.68 (89)
T4 (µg/dL)	2.56 ± 0.82	2.45 ± 0.85	3.44 ± 0.69	3.42 ± 0.81* (134)	2.02 ± 0.27	2.16 ± 0.45	1.74 ± 0.30	2.23 ± 0.60
TSH (ng/mL)	2.25 ± 0.90	2.26 ± 0.64	3.60 ± 2.79	9.11 ± 11.38 (405)	2.61 ± 0.70	3.33 ± 1.91	2.87 ± 1.31	5.49 ± 6.37 (210)
rT3 (ng/mL)	0.09 ± 0.03	0.09 ± 0.05	0.09 ± 0.04	0.19 ± 0.05** (211)	012 ± 0.04	014 ± 0.06	0.09 ± 0.02	0.33 ± 0.16** (275)
Week 104								
T3 (ng/dL)	49.79 ± 21.02	52.77 ± 20.97	50.01 ± 20.80	44.28 ± 15.86 (89)	72.72 ± 32.39	70.90 ± 19.28	65.93 ± 23.96	64.82 ± 22.16 (89)
T4 (µg/dL)	2.25 ± 0.73	2.27 ± 0.73	2.24 ± 0.97	2.50 ± 0.58	1.55 ± 0.99	1.56 ± 0.69	1.96 ± 0.75	2.47 ± 0.98** (159)
TSH (ng/mL)	2.38 ± 1.13	3.29 ± 1.61	3.48 ± 1.77	11.29 ± 14.92** (474)	2.52 ± 0.99	2.93 ± 1.78	3.78 ± 2.94	3.98 ± 6.28 (158)
rT3 (ng/mL)	0.03 ± 0.03	0.04 ± 0.03	0.04 ± 0.03	0.07 ± 0.05** (233)	0.05 ± 0.03	0.09 ± 0.04	0.20 ± 0.12**	0.24 ± 0.12** (480)

Data obtained from pages 3594-3599 of MRID 46512401

[a] Values are group means ± SD

[b] Numbers in parentheses are percent of control values calculated by the reviewer.

* p <0.05; ** p <0.01; all T4 and TSH as well as T3 and rT3 at 104 weeks analyzed using Dunnett's test; T3 and rT3 analyzed using the Kruskal-Wallis test at weeks 26 and 52

Table 10a. Inorganic Iodide Concentrations in Maternal Rabbits (Does) after MeI administration *via* the Inhalation Route

Maternal Exposure	Gestation Day/Time of sampling after start of daily exposure	Serum Iodide Concentrations (ng/mL)	
		Group 1 (0 ppm)	Group 2 (20 ppm MeI)
GD23	**GD23 3 hrs**	6.89 ± 2.28	7500 ± 488* (↑1089X)
	GD23 6 hrs	48.6 ± 56.6	9570 ± 4750* (↑197X)
GD23-24	**GD24 0 hrs§**	23.5 ± 19.7	1740 ± 1340 (↑74X)
	GD24 6 hrs	23.5 ± 13.4	14300 ± 2360* (↑609X)
GD23-25	**GD25 12 hrs**	14.3 ± 6.4	5110 ±1760* (↑357X)
	GD25 18 hrs	19.7 ± 11.4	4470 ± 3250* (↑227X)
GD23-26	**GD26 0 hrs§**	5.18 ± 0.09	3610 ±1200* (↑697X)
	GD26 6 hrs	10.5 ± 7.0	16600 ± 6800* (↑1581X)

Excerpted from Appendix I pp. 438-453 (MRID 46451002)
§ t=0 hrs. indicates that sampling was conducted prior to daily exposure
* Statistically different ($p<0.05$) from control
Numbers presented parenthetically represent change from control.

Table 10b. Inorganic Iodide Concentrations in Rabbit Fetuses after maternal MeI administration *via* the Inhalation Route

Fetal Exposure	Gestation Day/Time of sampling after start of daily exposure	Serum Iodide Concentrations (ng/mL)	
		Group 1 (0 ppm)	Group 2 (20 ppm MeI)
GD23	**GD23 3 hrs**	114 ± 14	15100 ± 4620* (↑132X)
	GD23 6 hrs	179 ± 77	27800 ± 9250* (↑155X)
GD23-24	**GD24 0 hrs§**	155 ± 24	8960 ± 4830* (↑58X)
	GD24 6 hrs	154 ± 11	33200 ± 11900* (↑216X)
GD23-25	**GD25 12 hrs**	161 ± 16	40100 ± 15700* (↑249X)
	GD25 18 hrs	217 ± 55	32000 ± 12800* (↑147)
GD23-26	**GD26 6 hrs**	171 ± 66	72600 ± 23200* (↑425X)

Excerpted from Appendix I pp. 438-453 (MRID 46451002)
§ t=0 hrs. indicates that sampling was conducted prior to daily exposure
* Statistically different ($p<0.05$) from control
Numbers presented parenthetically represent change from control.

Table 10c. Rabbit Maternal (Does) Thyroid/Pituitary Hormone Concentrations in Serum			
Maternal Exposure (Time of Euthanasia After Initiation of Daily Exposure)		**Hormone Concentration**	
		Group 1 (0 ppm)	**Group 2 (20 ppm MeI)**
GD23 (6 hr)	**TSH (ng/mL)**	0.5 ± 0.10	0.52 ± 0.19
	T3 (ng/dL)	180 ± 23.8	173 ± 12.3
	T4 (µg/dL)	1.76 ± 0.27	1.75 ± 0.40
GD24 (6 hr)	**TSH (ng/mL)**	0.46 ± 0.11	0.62 ± 0.04* (↑35%)
	T3 (ng/dL)	173 ± 16.4	158 ± 19.7 (↓9%)
	T4 (µg/dL)	1.43 ± 0.42	1.44 ± 0.46
GD 25 (12 hr)	**TSH (ng/mL)**	0.56 ± 0.05	0.68 ± 0.20 (↑21%)
	T3 (ng/dL)	160 ± 36.3	136 ± 33.6 (↓15%)
	T4 (µg/dL)	1.33 ± 0.24	0.95 ± 0.85 (↓29%)
GD26 (6 hr)	**TSH (ng/mL)**	0.58 ± 0.24	0.58 ± 0.15
	T3 (ng/dL)	122 ± 24.2	114 ± 25.0 (↓7%)
	T4 (µg/dL)	0.60 ± 0.38	0.84 ± 0.89 (↑40%)
GD29	**TSH (ng/mL)**	0.56 ± 0.11	1.05 ± 0.65 (↑88%)
	T3 (ng/dL)	168 ± 29.7	150 ± 18.2 (↓11%)
	T4 (µg/dL)	0.77 ± 0.35	0.40 ± 0.36 (↓48%)

Excerpted from Appendix H, Table 1, page 380 (MRID 46451002)
[a]Numbers presented parenthetically represent % change from control
* Statistically different ($p<0.05$) from control

Table 10d. Rabbit Fetal Thyroid/Pituitary Hormone Concentrations in Serum			
Fetal Exposure (Time of Euthanasia After Initiation of Daily Exposure)		**Hormone Concentrations**	
		Group 1 (0 ppm)	**Group 2 (20 ppm MeI)**
GD23 (0 hr)	**TSH (ng/mL)**	1.2 ± 0.1	1.1 ± 0.2
	T3 (ng/dL)	10.1 ± 5.19	8.9 ± 5.38 (↓12%)[a]
	T4 (µg/dL)	0.12 ± 0.12	0.07 ± 0.02 (↓42%)
GD23 (6 hr)	**TSH (ng/mL)**	1.2 ± 0.4	1.1 ± 0.2
	T3 (ng/dL)	4.5 ± 2.55	6.5 ± 4.77 (↑44%)
	T4 (µg/dL)	0.07 ± 0.03	0.10 ± 0.05 (↑43%)
GD24 (0 hr)	**TSH (ng/mL)**	1.5 ± 0.2	1.0 ± 0.2* (↓33%)
	T3 (ng/dL)	11.3 ± 4.27	10.1 ± 6.34 (↓11%)
	T4 (µg/dL)	0.09 ± 0.05	0.03 ± 0.03 (↓67%)
GD24 (6 hr)	**TSH (ng/mL)**	1.9 ± 0.5	1.7 ± 0.4
	T3 (ng/dL)	10.4 ± 2.01	13.6 ± 4.63 (↑31%)
	T4 (µg/dL)	0.05 ± 0.04	0.08 ± 0.05 (↑60%)
GD 25 (12 hr)	**TSH (ng/mL)**	1.7 ± 0.4	2.7 ± 0.6 (↑59%)
	T3 (ng/dL)	13.1 ± 6.50	13.3 ± 5.76
	T4 (µg/dL)	0.20 ± 0.11	0.06 ± 0.09* (↓70%)
GD25 (18 hr)	**TSH (ng/mL)**	1.5 ±0.2	4.2 ± 1.1* (↑180%)
	T3 (ng/dL)	12.0 ± 2.44	13.2 ± 5.61 (↑10%)
	T4 (µg/dL)	0.08 ± 0.07	0.00 ± 0.00 (↓100%)
GD26 (6 hr)	**TSH (ng/mL)**	1.9 ± 0.9	5.1 ± 1.5* (↑168%)
	T3 (ng/dL)	15.4 ± 3.09	26.6 ± 12.62 (↑73%)
	T4 (µg/dL)	0.06 ± 0.04	0.03 ± 0.05 (↓50%)
GD29	**TSH (ng/mL)**	1.1 ± 0.2	4.4 ± 3.4* (↑300%)
	T3 (ng/dL)	23.9 ± 4.85	49.4 ± 30.17 (↑107%)
	T4 (µg/dL)	0.14 ± 0.04	0.10 ± 0.15 (↓29%)

Excerpted from Appendix H, Table 2, page 381 (MRID 46451002)
[a]Numbers presented parenthetically represent % change from control
* Statistically different ($p<0.05$) from control

TABLE 11. Serum hormone levels in male and female mice fed microencapsulated iodomethane				
Parameter	**Dietary concentration (ppm)**			
	0	**60**	**200**	**600**
Males				
T_3 (ng/dL)	71.49 ± 16.686[a]	70.46 ± 17.864	74.86 ± 13.762	74.99 ± 13.520
T_4 (µg/dL)	2.68 ± 0.742	2.60 ± 0.976	2.55 ± 0.942	1.87 ± 0.570** (70)[b]
TSH (µg/mL)	0.45 ± 0.140	0.54 ± 0.210	0.69 ± 0.277* (153)	0.86 ± 0.468** (191)
Females				
T_3 (ng/dL)	62.17 ± 17.453	58.76 ± 10.346	67.27 ± 22.063	68.81 ± 18.407
T_4 (µg/dL)	1.82 ± 0.996	1.91 ± 0.951	1.87 ± 0.843	1.76 ± 0.753
TSH (µg/mL)	0.28 ± 0.107	0.45 ± 0.306	0.47 ± 0.198	0.39 ± 0.190

Data taken from Table 32 and 33 (pp. 265-266), MRID 46582801.
[a]Mean ± standard deviation
[b]Numbers in parentheses are percent of control calculated by the reviewer.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE EVIDENCE

1. Carcinogenicity

Evidence of carcinogenicity was seen in the thyroid glands of male rodents (Sprague-Dawley rats and CD-1 mice) in the standard bioassays. Though a slight increase in the incidence of uterine and cervical tumors was reported for female mice, these lesions were not considered compound related (see rationale below).

Rat

In Sprague-Dawley male rats, thyroid follicular cell tumors (adenomas and carcinomas) noted at the highest concentration tested (60 ppm) were considered to be treatment related since:

- there were significant positive trends for all three types (adenomas, $p<0.01$; carcinomas, $p<0.05$; combined adenomas/carcinomas, $p<0.01$), as well as significant differences in the pair-wise comparisons of the 60 ppm dose group with the controls for adenomas (10/42, 24% $p<0.01$, vs 2/45, 4% controls) and combined adenomas and/or carcinomas, (12/42, 29% $p<0.05$ vs. 4/45, 9% controls)
- the incidences at the high dose exceeded the historical control ranges for adenomas (1.67-12%) and for carcinomas (0.87-3.85%)

The committee concluded that the dose levels tested were adequate and not excessive in both sexes since there was evidence of non-neoplastic lesions, thyroid/pituitary hormone changes, body weight and body weight gain decreases.

Mice

In the **CD-1 mice**, **thyroid follicular cell tumors** were observed in males only. These tumors were considered to be treatment-related because:

- there was a significant positive trend for combined adenomas/carcinomas ($p<0.05$)
- the increased incidence of thyroid tumors is consistent with the observations in the Sprague-Dawley rats
- the incidences exceeded the historical control range for adenomas (0-2%), although not for carcinomas (0-2%)
- an increase in thyroid tumorigenesis is consistent with substantial sustained perturbations of thyroid/pituitary hormone homeostasis as seen after iodomethane exposure

A slight increase in the incidence of **uterine and cervical fibromas** was observed in female CD-1 mice. Although significant positive trends for cervical fibromas ($p<0.05$) and combined cervical/uterine fibromas ($p<0.01$) were reported, the lesions were not considered to be treatment-related for the following reasons:

- Microscopic in size
- Occurred only at the terminal sacrifice
- Had no precursor lesions (hyperplasia)
- Not found in the rat bioassay
- Fibromas, consisting primarily of collagen fibers, have not been associated with chemical carcinogenicity.
- Moreover, these types of lesions are not uncommon in the reproductive tract of female mice of this age.
  - A comparison with historical control data was not appropriate since the number of tissue samples examined in this study far exceeded the customary number of sections evaluated for historical control data.

The committee concluded that the dose levels tested in this study were adequate to assess the carcinogenicity potential of iodomethane based on the increased incidence of non-neoplastic lesions in the thyroid, esophagus, pharynx, stomach, and pituitary, decreased body weights (↓6-11%, $p<0.01$) and body weight gains (↓21-92%, $p<0.01$), as well as changes in serum thyroid/pituitary hormone levels.

2. Mutagenicity

Although the guideline mutagenicity studies submitted by the registrant are negative for genotoxicity, there is concern that appropriate measures to prevent compound volatilization may not have been taken. In particular, re-evaluation of the Bacterial Reverse Gene Mutation test (MRID 45593813) indicates that this is a "no test" since the study report did not describe what measures were taken, if any, to keep the test substance "in contact" with the cells.

Numerous studies in the open literature indicate that iodomethane is a methylating agent and consequently a potential mutagen. Evidence of this mutagenic potential is available from numerous *in vitro* assays and one *in vivo* assay (*e.g., S. typhimurium, E. coli,*CHO cells, mouse lymphoma assay, and an *in vivo* DNA adduct formation test).

3. Structure Activity Relationship

Methyl bromide (MeBr), a monohalogenated methane like iodomethane, was considered with regards to its SAR to iodomethane. MeBr was classified as "not likely to be carcinogenic to humans" based on the lack of tumorigenic response in two rodent bioassays in spite of several positive mutagenicity assays. Iodinated glycerol (which contains 3-iodo-1,2-propanediol as its major component), a close structural analog of iodomethane, is an alkyl iodide with alkylating and mutagenic activities and has been shown to induce the same type of thyroid tumors as iodomethane. However, iodinated glycerol is a multi-target carcinogen (including port of entry) whereas iodomethane's carcinogenic effect seems to be confined to the thyroid gland in rodents. In contrast, a number of nongenotoxic iodinated compounds with little or no structural similarity to iodomethane (e.g., amiodarone, potassium iodide) have been shown to elicit similar thyroid carcinogenic effects as iodomethane suggesting that iodide may be the key common link for the thyroid activity.

4. Mode of Action

There is compelling evidence indicating that iodomethane induces thyroid follicular cell tumors through an antithyroidal MOA. Although iodomethane has been shown to be mutagenic primarily in *in vitro* studies and produced DNA adducts in one study in rats, the weight-of-evidence (WOE) indicates that perturbation of thyroid homeostasis is the key event in the thyroid tumorigenic response observed after iodomethane exposure.

Among the evidence supporting an antithyroidal MOA is the observation that only male rodents exhibit increases in thyroid tumors. This is a common response pattern for classical antithyroidal agents. In addition, the increases of cell growth *in vivo* (*e.g.,* increases in thyroid weights and hyperplasia) progressing to follicular cell tumors were only seen in the presence of thyroid/pituitary hormone changes (decreased T_3 and T_4 in conjunction with profound TSH increases) thus exhibiting a pattern of both dose and temporal concordance. In a 1998 review article, Hard states that "genotoxic chemicals able to induce thyroid cancer in rodents have different morphological and physiological effects from those of known goitrogens." Characteristics of goitrogen-induced

tumors include: (i) diffuse follicular cell hyperplasia, (ii) increases in thyroid weights preceding tumor formation, (iii) sustained increases in serum TSH levels, and (iv) changes in serum T_4 levels. In contrast, mutagen-induced thyroid tumors involve the formation of focal atypical hyperplasia (originating from single follicles) and do not involve changes in thyroid/pituitary hormone economy or changes in thyroid weights unrelated to tumor development.[6] The fact that iodomethane exposure leads to a dramatic increase in serum iodide levels coupled with the changes in thyroid/pituitary hormone levels, thyroid weights, and diffuse follicular cell hyperplasia points to an intrathyroidal site of action further supported by the fact that excess iodide is widely recognized as a goitrogenic agent.[7]

Evidence suggesting that a mutagenic MOA may be operative in the iodomethane thyroid tumor response include positive results in *in vitro* gene mutation and chromosome aberration assays as well as formation of methyl DNA adducts in the liver, lung, forestomach and stomach of rats (thyroid not examined) following oral or inhalation exposure. In contrast, several lines of evidence indicate that mutagenicity is not the MOA for thyroid follicular cell tumor formation. For instance, the majority of the neoplastic lesions observed after iodomethane exposure were benign and were observed at the terminal sacrifice unlike tumors induced through a mutagenic MOA. Other aspect that contradicts a mutagenic MOA is that although DNA adducts are found in multiple organs (*e.g.*, liver, lungs, forestomach) tumors are only seen in the thyroid in the rodent bioassays. This is consistent with the observation that in standard rodent bioassays, no thyroid carcinogen acting by a mutagenic MOA has been identified that does not induce tumors at multiple sites. SAR also points to a non-mutagenic MOA for thyroid tumorigenesis since (i) methyl bromide - a methylating and mutagenic agent - structurally related to iodomethane did not show evidence of tumorigenesis in any of the rodent bioassays and (ii) non-genotoxic iodinated compounds elicit a similar pattern of thyroid tumor formation in the absence of tumors at other sites. Furthermore, the incidence of neoplastic lesions attributed to chlorate and perchlorate - two non-mutagenic thyroid carcinogens with an antithyroidal site of action - is similar to what is observed after iodomethane exposure. Finally, the lack of a tumorigenic response at the port-of-entry (respiratory tract) in the Inhalation Combined Chronic/Carcinogenicity study in rats also demonstrates that mutagenicity is not contributing to the carcinogenic profile of iodomethane since tumors in the respiratory tract (particularly the nasal cavity) would be expected if iodomethane were acting through a mutagenic MOA.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), the CARC classified Iodomethane as “Not likely to be Carcinogenic to humans at doses that do not

---

[6] Hard, G.C. (1998). *Recent Developments in the Investigation of Thyroid Regulation and Thyroid Carcinogenesis.* Environ. Health Perspect. **106(8):**427-436.

[7] *Toxic Responses of the Endocrine System* in Casarett & Doull’s Toxicology The Basic Science of Poisons. Fifth edition (1995), Curtis D. Klaassen, ed.

alter rat thyroid hormone homeostasis." This was based on the evidence that rats are substantially more sensitive than humans to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance. The committee concluded that the key event that influences the thyroid tumor response is the sustained stimulation of cell proliferation by TSH consistent with the increase in thyroid follicular cell tumors only.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The point of departure for the iodomethane long-term inhalation risk assessment will be based on salivary gland metaplasia. This endpoint is more sensitive than the effects on thyroid hormone homeostasis; the human equivalent concentration NOAELs (HEC_{NOAEL}) calculated for the effect are (0.89 ppm and 3.75 ppm, for non-occupational and occupational risk assessments, respectively). In contrast, the HEC_{NOAELs} calculated for thyroid hormone perturbations using the PBPK model submitted by the registrant are ≈ 6.6 ppm and 26 ppm for non-occupational exposures and occupational exposures, respectively.[8] Consequently, the use of the salivary gland and port-of-entry effects for risk assessment purposes will be protective of the effects on thyroid hormone homeostasis which may lead to other non-cancer adverse health outcomes (*e.g.*, goiter and neurodevelopmental deficits).

[8] Mileson, B.E. *et. al.* (2005). *Risk Assessment of Thyroid Follicular Cell Tumors in Rats Following 2-year Iodomethane Exposure by Inhalation.*

VIII. BIBLIOGRAPHY

MRID No.	CITATION
	Brunsman, L (2005) Iodomethane Qualitative Risk Assessment Based on Crl:CD(SD)IGS BR rat inhalation study
	Brunsman, L (2005) Iodomethane Qualitative Risk Assessment Based on Crl:CD®1(ICR) Mouse Dietary Study
	Hard, G.C. (1998). *Recent Developments in the Investigation of Thyroid Regulation and Thyroid Carcinogenesis.* Environ. Health Perspect. 106(8):427-436.
46582801	Harriman, J. (2005) An 18-Month Dietary Carcinogenicity Study of Microencapsulated Iodomethane in Mice: Final Report. Project No. WIL/418025. Unpublished study prepared by WIL Research Laboratories, Inc.
46512401	Kirkpatrick, D. (2005) A 24-Month Inhalation Combined Chronic Toxicity/Carcinogenicity Study of Iodomethane in Rats: Final Report. Project No. WIL/418019, 318019M. Unpublished Study Prepared by WIL Research Laboratories, Inc.
	McCarroll, N. (2005). Iodomethane: Review of Iodomethane Mutagenicity Studies
46512402	Mileson, B.E. *et. al.* (2005). Risk Assessment of Thyroid Follicular Cell Tumors in Rats Following 2-year Iodomethane Exposure by Inhalation. Project No. 810/03. Unpublished study prepared by Technology Sciences Group, Inc. and Universitaet Dortmund and Institute of Environmental Toxicology.
46601701	Mileson, B.E. *et al.* (2005). Review of Iodomethane Mutagenicity Studies. Project 34505. Unpublished study prepared by Arysta LifeScience North America Corporation and Technology Services Group, Inc.
	Pisarev MA, Gartner R (2000). *Autoregulatory actions of iodine.* In: Braverman LE, Utiger RD eds. Werner and Ingbar's the thyroid: A fundamental and clinical text. Pp 85-90
	Poirier, LA *et al.*, (1975) "Bioassay of Alkyl Halides and Nucleotide Base Analogs by Pulmonary Tumor Response in Strain A Mice" *Cancer Res.* **35:**1411-1415

42451002 Sloter, E. (2005) Mode of Action Study for Iodomethane-Related Fetotoxicity in Rabbits: Final Report. Project No.: WIL/418032, DUPONT/15855, P0000903. Unpublished study prepared by WIL Research Laboratories, Inc. and E.I. du Pont de Nemours and Company, Inc. and Exygen Research

46610901 Sweeney, L. and B. Mileson (2005). Application of PBPK Modeling of Iodomethane in Rat Cancer Risk Assessment. Project No. 34502. Unpublished study prepared by Sapphire Group, Inc.

Toxic Responses of the Endocrine System in Casarett & Doull's Toxicology The Basic Science of Poisons. Fifth edition (1995), Curtis D. Klaassen, ed.

USEPA (1998) *Assessment of Thyroid Follicular Cell Tumors* Office of Research and Development, Risk Assessment Forum; EPA report no. EPA/630/R-97/002